(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 April 2002 (25.04.2002)

PCT

(10) International Publication Number
WO 02/32408 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/EP01/12075

(22) International Filing Date: 18 October 2001 (18.10.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/242,036 20 October 2000 (20.10.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/32408 A2

(54) Title: COMPOSITIONS

(57) Abstract: Disclosed are methods for the treatment of conditions associated with elevated levels of Lp(a), such as CHD, ischaemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, reduction in necrosis after myocardial infarction, dyslipidemia and post-prandial lipemia. The methods include administration of a therapeutically effective amount of a pharmaceutical combination of a thyromimetic compound and a statin.

COMPOSITIONS

There are several forms of circulating blood cholesterol which occur naturally in mammals. Some forms are considered "bad" cholesterol, while other forms are considered "good" cholesterol and are essential for good health. The good form of cholesterol has been established to be high density lipoprotein (HDL). Low density lipoprotein (LDL) is a "bad" cholesterol.

Lowering LDL, the bad form of cholesterol, is now one of the primary objectives of physicians treating patients who have, or who have a high risk of developing, cardiovascular diseases such as coronary heart disease, atherosclerosis, myocardial infarction, stroke, cerebral infarction, and even restenosis following balloon angioplasty. Many physicians are now utilizing cholesterol lowering agents purely as a prophylactic treatment in healthy subjects whose cholesterol levels are normal, thereby guarding against development of cardiovascular diseases.

The most commonly used cholesterol lowering agents are the statins, which are compounds which inhibit the enzyme 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, the enzyme responsible for catalyzing the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the cholesterol biosynthetic pathway.

Another form of LDL cholesterol, the primary bad form, is a modified form of LDL called lipoprotein(a), or "Lp(a)". Elevated levels of Lp(a) are believed to be detrimental and associated with a higher risk for coronary heart disease (CHD). Lowering of Lp(a) levels with a combination of estrogen and progesterone is associated with a lower incidence of detrimental coronary events.

Treatment with statins has been shown to significantly increase Lp(a) levels or have no effect at all on Lp(a) levels. Treatment with fluvastatin has further been shown not to decrease the levels of Lp(a) in man.

On the other hand, treatments for the reduction of Lp(a) levels are known and include thyroid hormone which lowers Lp(a) in humans. Moreover, a synthetic thyromimetic compound has also been shown to lower Lp(a) by 42% in a non-human primate. However, heretofore, there has not been a pharmaceutical composition and method which acts to

further reduce Lp(a) levels below that achieved by the administration of thyromimetic compounds alone.

For the foregoing reasons, there is a need for new therapeutic methods and compositions for more effective lowering of Lp(a) levels for treatment of conditions associated with elevated levels of Lp(a).

Toward these ends and others, in one aspect the present invention there is provided a method of treating conditions associated with elevated Lp(a) levels comprising administering a therapeutically effective amount of a pharmaceutical combination comprising a thyromimetic agent and a statin to a subject in need thereof. Conditions associated with elevated Lp(a) levels include CHD, ischaemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, reduction in necrosis after myocardial infarction, dyslipidemia and post-prandial lipemia. The therapeutically effective amount of pharmaceutical combination above may be administered in combination with a pharmaceutically acceptable carrier to form a pharmaceutical composition.

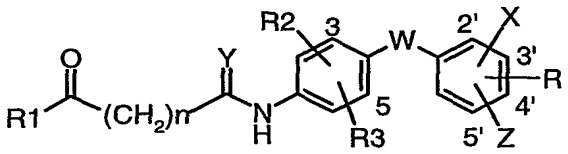
The combinations of this invention can also employ the pharmaceutically acceptable salts of the respective active compounds.

Another aspect of the present invention provides pharmaceutical compositions comprising the pharmaceutical combination described above further comprising a pharmaceutically acceptable carrier.

Another aspect of the present invention provides the use of combination a thyromimetic agent and a statin for the manufacture of a medicament for the treatment of conditions associated with elevated Lp(a) levels.

Preferred thyromimetic compounds to be employed in the pharmaceutical combinations of the present invention include those disclosed in EP 580 550, U. S. Patent Nos. 5654468, 5569674 and 5401772 which are incorporated herein by reference as if set forth in their entirety.

Particularly preferred thyromimetic compounds also include compounds of formula I



(I)

in which

W is O, S, S(O) or $S(O)_2$;

X is -SR4, -S(O)R4, -$S(O)_2$R4, or -$S(O)_2$NR5R6; or X is -C(O)NR5R6 provided that -C(O)NR5R6 is located at the 3'-, 4'- or 5'-position;

Y is O or H_2;

Z is hydrogen, halogen, hydroxy, optionally substituted alkoxy, aralkoxy, acyloxy or alkoxycarbonyloxy;

R is hydrogen, halogen, trifluoromethyl, lower alkyl or cycloalkyl;

R1 is hydroxy, optionally substituted alkoxy, aryloxy, heteroaryloxy, aralkoxy, cycloalkoxy, heteroaralkoxy or -NR5R6;

R2 is hydrogen, halogen or alkyl;

R3 is halogen or alkyl;

R4 is optionally substituted alkyl, aryl, aralkyl, heteroaralkyl or heteroaryl;

R5, R6 and R7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R5 and R6 combined are alkylene optionally interrupted by O, S, S(O), $S(O)_2$ or NR7 which together with the nitrogen atom to which they are attached form a 5- to 7- membered ring;

n represents zero or an integer from 1 to 4; and pharmaceutically acceptable salts thereof.

An even more preferred thyromimetic compound is N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid.

Typical statins to be employed in combination with the compound of Formula I include pitavastatin, atorvastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, lovastatin, dalvastatin, rosuvastatin and fluindostatin. The statins can be employed as pharmaceutically acceptable salts, for example, atorvastatin calcium. The most preferred statin is pitavastatin, fluvastatin and simvastatin, such that the most preferred pharmaceutical combination of the present invention is N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid and a statin selected from the group consisting of pitavastatin, fluvastatin and simvastatin.

Other objects, features, advantages and aspects of the present invention will become apparent to those of skill from the following description, appended claims and accompanying drawings. It should be understood, however, that the following description, appended claims, drawings and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following.

Definitions

Unless otherwise specified herein, common definitions are intended by the words and terms used herein. As throughout this specification the singular is intended to include the plural and vice versa.

For example, the term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed (or free) combinations of the active ingredients.

The term "fixed combination" as that term is used herein means that the active compounds are both administered to a patient simultaneously in the form of a single entity or dosage. As an example, a fixed combination would be one capsule containing two active compounds.

The term "non-fixed combination" as that term is used herein means that the active compounds are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body at the same time. As an example, a non-fixed combination would be two capsules each containing one active

ingredient where the purpose is to have the patient achieve treatment with both active ingredients together in the body.

The term "therapeutically effective amount" shall mean that amount of compound that will elicit the biological or medical response of a tissue, system or animal (mammal) that is being sought by a researcher or clinician.

The terms "mammal", "mammalian organism", "subject" or "patient" are used interchangeably herein and include, but are not limited to, humans, dogs, cats, horses and cows. The preferred patients are humans.

The term "treat" or "treatment" encompasses the complete range of therapeutically positive effects associated with pharmaceutical medication including reduction of, alleviation of and relief from the symptoms or illness, which affect the organism. When treating conditions associated with elevated levels of Lp(a), treatment includes the administration of compounds to lower Lp(a) levels in the patient suffering from the condition to a level below that achieved by administration of thyromimetic compounds alone.

The term "elevated levels of Lp(a)" as used herein shall mean levels of Lp(a) which subjects the patient to the risk of vascular, particularly cardiovascular diseases, mediated by Lp(a), including but not limited to CHD, ischaemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, reduction in necrosis after myocardial infarction, dyslipidemia and post-prandial lipemia.

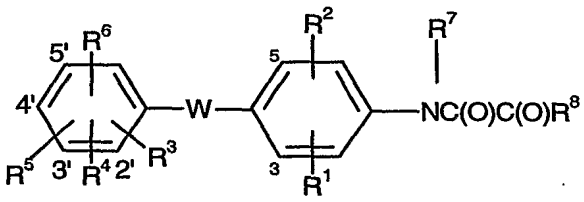
As stated above, administering a thyromimetic compound of the present invention to a mammal decreases levels of Lp(a) by approximately 42% and, conversely, administration of statin to the same mammal does not lower levels of Lp(a). Applicants, however, have surprisingly found that administration of a thyromimetic compound in combination with a statin reduces levels of Lp(a) in mammals greater than that achieved by administration of thyromimetic compounds alone.

Accordingly, an aspect of the present invention provides a method of reducing Lp(a) levels in mammals comprising administering to a mammal in need thereof a pharmaceutical combination comprising a thyromimetic compound and a statin. Particularly, the levels of Lp(a) are lowered to a level below that achieved by administration of thyromimetic compounds alone.

Another aspect of the present invention provides a method of treating conditions associated with elevated levels of Lp(a) in mammals comprising administering to a mammal in need thereof a therapeutically effective amount of a pharmaceutical combination comprising a thyromimetic compound and a statin to achieve a therapeutic effect which is greater than that achieved by the administration of a thyromimetic compound or a statin alone. Conditions associated with elevated levels of Lp(a) include CHD, ischaemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, reduction in necrosis after myocardial infarction, dyslipidemia and post-prandial lipemia.

Thyromimetic compounds of the present invention include those compounds disclosed in EP 580 550, U. S. Patent Nos. 4069343; 4554290; 4766121; 4826876; 4910305; 5061798; 5232947; 5284971; 5401772; 5569674 and 5654468, WO 00/58279, and those disclosed in Yokoyama N. et al., Journal of Medicinal Chemistry, 38(4):695-707 (1995) and Stephan Z. F. et al., Atherosclerosis, 126:53-63 (1996), all of which are incorporated herein in their entirety as if set forth in full herein, especially the corresponding subject matter of the claims and the working examples directed to thyromimetic compounds.

Preferred thyromimetic compounds include those disclosed in WO 00/51971 of the formula



prodrugs thereof, geometric and optical isomers thereof, and pharmaceutically acceptable salts of said compounds, said prodrugs, and said isomers, wherein:

R^1, R^2 and R^3 are each independently hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl, -CN, $-OCF_3$ or $-OC_{1-6}$ alkyl;

R^4 is hydrogen, C_{1-12} alkyl optionally substituted with one to three substitutents independently selected from Group Z, C_{2-12} alkenyl, halogen, -CN, aryl, heteroaryl, C_{3-10} cycloalkyl, heterocycloalkyl, $-S(O)_2NR^9R^{10}$, $-C(O)NR^9R^{10}$, $-(C_{1-6}$ alkyl)$-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$, $-(C_{1-6}$ alkyl)$-OR^{11}$, $-OR^{11}$or $-S(O)_aR^{12}$, provided that, where

R^5 is not fluoro, R^4 is $-S(O)_2NR^9R^{10}$, $-C(O)NR^9R^{10}$, $-(C_{1-6}$ alkyl$)-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$, $-(C_{1-6}$ alkyl$)-OR^{11}$, $-OR^{11}$or $-S(O)_aR^{12}$;

or R^3 and R^4 may be taken together to form a carbocyclic ring A of the formula $-(CH_2)_b-$ or a heterocyclic ring A selected from the group consisting of $-Q-(CH_2)_C-$ and $-(CH_2)_j-Q-(CH_2)_k-$ wherein Q is O, S or NR^{17}, wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C_{1-4} alkyl, halide or oxo;

R^5 is fluoro, hydroxy, C_{1-4} alkoxy or $OC(O)R^9$;

or R^4 and R^5 may be taken together to form a heterocyclic ring B selected from the group consisting of $-CR^9=CR^{10}$ -NH-, $-N=CR^9-NH-$, $-CR^9=CH-O-$ and $-CR^9=CH-S-$;

R^6 is hydrogen, halogen, C_{1-4} alkyl or trifluoromethyl;

R^7 is hydrogen or C_{1-6} alkyl;

R^8 is $-OR^9$ or $-NR^{19}R^{20}$;

R^9 and R^{10} for each occurrence are independently (A) hydrogen, (B) C_{1-12} alkyl optionally substituted with one or more substituents independently selected from Group V, (C) C_{2-12} alkenyl, (D) C_{3-10} cycloalkyl optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-5} alkynyl, C_{3-10} cycloalkyl, -CN, $-NR^{13}R^{14}$, oxo, $-OR^{18}$, $-COOR^{18}$ or aryl optionally substituted with X and Y, (E) aryl optionally substituted *with X and Y, or (F) het optionally substituted with X and Y;*

or R^9 and R^{10} for any occurrence may be taken together to form a heterocyclic ring C optionally further containing a second heterogroup selected from the group consisting of -O-, $-NR^{13}-$ and -S-, *and optionally further substituted with one or more substituents* independently selected from C_{1-5} alkyl, oxo, $-NR^{13}R^{14}$, $-OR^{18}$, $-C(O)_2R^{18}$, -CN, $-C(O)R^9$, aryl optionally substituted with X and Y, het optionally substituted with X and Y, C_{5-6} spirocycloalkyl, and a carbocyclic ring B selected from the group consisting of 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated carbocyclic rings, and including any bicyclic group in which said carbocyclic ring B is fused to a carbocyclic ring C selected from the group consisting of 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated carbocyclic rings;

R^{11} is C_{1-12} alkyl optionally substituted with one or more substituents independently selected from Group V, C_{2-12} alkenyl, C_{3-10} cycloalkyl, trifluoromethyl, difluoromethyl, monofluoromethyl, aryl optionally substituted with X and Y, het optionally substituted with X and Y, $-C(O)NR^9R^{10}$ or $-C(O)R^9$;

R^{12} is C_{1-12} alkyl optionally substituted with one or more substituents independently selected from Group V, C_{2-12} alkenyl, C_{3-10} cycloalkyl, aryl optionally substituted with X and Y, or het optionally substituted with X and Y;

R^{13} and R^{14} for each occurrence are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, $-(C_{1-6}$ alkyl)-C_{1-6} alkoxy, aryl optionally substituted with X and Y, het optionally substituted with X and Y, $-(C_{1-4}$ alkyl)-aryl optionally substituted with X and Y, $-(C_{1-4}$ alkyl)-heterocycle optionally substituted with X and Y, $-(C_{1-4}$ alkyl)-hydroxy, $-(C_{1-4}$ alkyl)-halo, $-(C_{1-4}$ alkyl)-poly-halo, $-(C_{1-4}$ alkyl)-$CONR^{15}R^{16}$ or C_{3-10} cycloalkyl;

R^{15} and R^{16} for each occurrence are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl or aryl optionally substituted with X and Y;

R^{17} is hydrogen, alkyl, C_{1-6} alkyl, $-COR^9$ or $-SO_2R^9$;

R^{18} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, $-(C_{1-6}$ alkyl)-C_{1-6} alkoxy, aryl optionally substituted with X and Y, het optionally substituted with X and Y, $-(C_{1-4}$ alkyl)-aryl optionally substituted with X and Y, $-(C_{1-4}$ alkyl)-heterocycle optionally substituted with X and Y, $-(C_{1-4}$ alkyl)-hydroxy, $-(C_{1-4}$ alkyl)-halo, $-(C_{1-4}$ alkyl)-poly-halo, $-(C_{1-4}$ alkyl)-$CONR^{15}R^{16}$, $-(C_{1-4}$ alkyl)-$(C_{1-4}$ alkoxy) or C_{3-10} cycloalkyl;

R^{19} is hydrogen or C_{1-6} alkyl;

R^{20} is hydrogen or C_{1-6} alkyl;

W is 0, $S(O)_d$, CH_2 or NR^9;

Group Z is C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-CF_3$, $-OCF_3$, hydroxy, oxo, -CN, aryl, heteroaryl, C_{3-10} cycloalkyl, heterocycloalkyl, $-S(O)_aR^{12}$, $-S(O)_2NR^9R^{10}$, $-C(O)R^9R^{10}$, and $-NR^9R^{10}$;

Group V is halogen, $-NR^{13}R^{14}$, $-OCF_3$, $-OR^9$, oxo, trifluoromethyl, -CN, C_{3-10} cycloalkyl, aryl optionally substituted with X and Y, and het optionally substituted with X and Y;

het for each occurrence is a heterocyclic ring D selected from the group consisting of 4-, 5-, 6-, 7-and 8-membered partially and fully saturated, and unsaturated, heterocyclic rings containing from one to four heteroatoms independently selected from the group consisting of N, O and S, and including any bicyclic group in which said heterocyclic ring D is fused to a benzene ring or a heterocyclic ring E selected from the group consisting of 4-, 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated, heterocyclic rings containing from one to four heteroatoms independently selected from the group consisting of N, O and S;

X and Y for each occurrence are independently (A) hydrogen, (B) halogen, (C) trifluoromethyl, (D) $-OCF_3$, (E) -CN, (F) C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, $-OCF_3$, $-CF_3$ and phenyl, (G) C_{1-6} alkoxy, (H) aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, $-OCF_3$, $-CF_3$, C_{1-4} alkyl and C_{1-4} alkoxy, (I) $-C(O)_2R^{13}$, (J) $-C(O)NR^{13}R^{14}$, (K) $-C(O)R^{13}$, (L) $-NR^{13}C(O)NR^{13}R^{14}$ and (M) $-NR^{13}C(O)R^{14}$; or X and Y for any occurrence in the same variable may be taken together to form (a) a carbocyclic ring D of the formula $-(CH_2)_e-$ or (b) a heterocyclic ring F selected from the group consisting of $-O(CH_2)_fO-$,$(CH_2)_gNH-$ and -CH=CHNH- ;

a and d are each independently 0, 1 or 2;

b is 3, 4, 5, 6 or 7;

c, f, g, j and k are each independently 2, 3, 4, 5 or 6; and

e is 3, 4, 5, 6 or 7.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, designated the A Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein W is O.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the A Group, designated the B Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 is located at the 3 position, R^2 is located at the 5 position, R^3 is located at the 2' position, R^4 is located at the 3' position, R^5 is located at the 4' position, and R^6 is located at the 5' position.

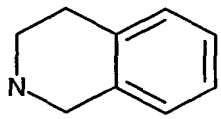
A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the B Group, designated the C Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 is hydrogen, or R^3 and R^4 are taken together to form a carbocyclic ring A of the formula $-(CH_2)_b-$ or a heterocyclic ring A selected from the group consisting of $-Q-(CH_2)_c$ and $-(CH_2)_j-Q-(CH_2)_k-$ wherein Q is O, S or NR^{17} wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C_{1-4} alkyl, halide or oxo, R^5 is hydroxy, R^6 is hydrogen and R^7 is hydrogen.

A preferred group of compounds pharmaceutically acceptable salts of such compounds, of the C Group, designated the D Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each independently methyl, bromo or chloro, and R^8 is hydroxy, methoxy, ethoxy, isopropoxy, NH_2 or $NH(CH_3)$.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the E Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $S(O)_2NR^9R^{10}$, and R^{10} is hydrogen or methyl.

Particularly preferred compounds of the E Group are compounds wherein (a) R^1 is chloro, R^2 is methyl, R^8 is ethoxy or hydroxy, R^9 is ethyl and R^{10} is hydrogen, (b) R^1 is chloro, R^2 is methyl, R^3 is ethoxy or hydroxy, R^9 is *n*-butyl and R^{10} is hydrogen, (c) R^1 is chloro, R^2 is methyl, R^8 is ethoxy or hydroxy, R^9 is $-CH_2$-cyclopropyl and R^{10} is hydrogen and (d) R^1 is chloro, R^2 is methyl, R^3 is isopropoxy or hydroxy, R^9 is cyclopropyl and R^{10} is hydrogen; and pharmaceutically acceptable salts of said compounds.

Another preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the F Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $S(O)_2NR^9R^{10}$, and R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_4$, $N(CH_2)_5$, morpholine or



Particularly preferred compounds of the F Group are those wherein R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_4$.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the E Group, designated the G Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is hydrogen, isopropyl, -CH_2-2-thienyl, -CH_2-cyclopropyl, cyclopropyl, -$(CH_2)_2OH$, exo-2-norbornyl, methyl, ethyl, 4-fluorophenyl, cyclobutyl, cyclopentyl, cyclohexyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-octyl or *n*-decyl.

Particularly preferred compounds of the G Group are compounds wherein (a) R^1 is chloro, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclopropyl and R^{10} is hydrogen, (b) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclopropyl and R^{10} is methyl, (c) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclobutyl and R^{10} is methyl, (d) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclopropyl and R^{10} is hydrogen and (e) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclobutyl and R^{10} is hydrogen; and pharmaceutically acceptable salts of said compounds.

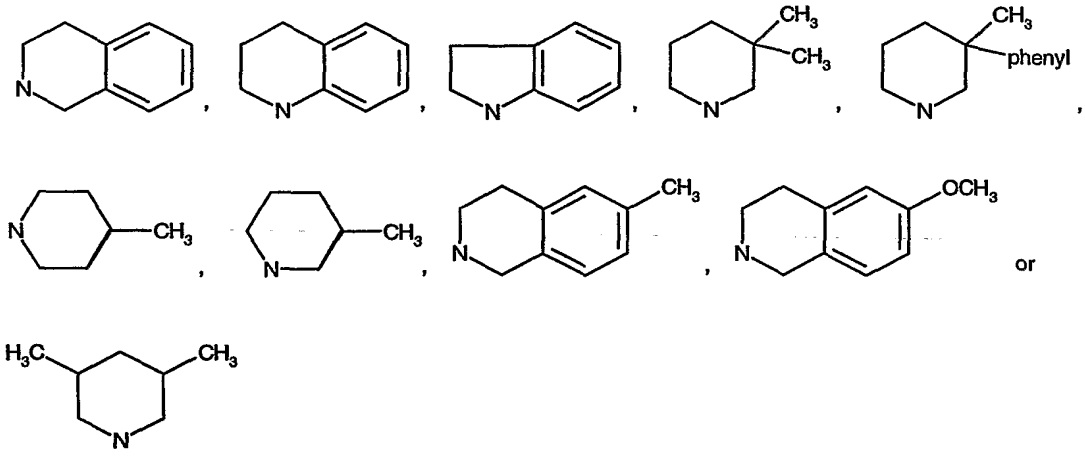
A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the J Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is -$C(O)NR^9R^{10}$, and R^{10} is hydrogen, methyl or ethyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the J Group, designated the K group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is methyl, ethyl, isopropyl, *n*-propyl, isobutyl, *n*-butyl, *n*-pentyl, *n*-hexyl, 4-fluorophenyl, -CH_2-2-thienyl, cyclopropyl, -CH_2-cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -CH_2-cyclohexyl, endo-2-norbornyl, exo-2-norbornyl, (S)-1-phenylethyl, (R)-1-phenylethyl, -CH_2-2-chlorophenyl, -CH_2-4-chlorophenyl, -CH_2-4-fluorophenyl, -CH_2-3-chloro-4-fluorophenyl, -CH_2-2-chloro-4-fluorophenyl, -CH_2-2-fluoro-4-chlorophenyl, -CH_2-3,4-difluorophenyl, -CH_2-4-isopropylphenyl, -CH_2-2,3-dichlorophenyl,

-CH_2-2,4-dichlorophenyl, -CH_2-3,4-dichlorophenyl, -CH_2-3-trifluoromethyl-4-chlorophenyl, 4-phenylphenyl, 3-(2,4-dimethyl)pentyl, (R)-1-(1-naphthyl)ethyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, (R)-1-(2-naphthyl)ethyl, (R)-2-(1-naphthyl)ethyl, -CH_2-(1-naphthyl), (R)-1-cyclohexylethyl, (S)-1-cyclohexylethyl, -CH_2-3,4-methylenedioxyphenyl, -CH_2-4-*t*-butylphenyl, -CH_2-2,3-dichlorophenyl, 1-indanyl, (R)-1-indanyl, (S)-1-indanyl, 5-indanyl, 1-(1,2,3,4-tetrahydronaphthyl) or (R)-1-cyclohexylethyl.

Particularly preferred compounds of the K Group are compounds wherein (a) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, R^9 is 3-(2,4-dimethyl)pentyl and R^{10} is hydrogen, (b) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclopropyl and R^{10} is methyl, (c) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is cyclobutyl and R^{10} is methyl, (d) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is 3-(2,4-dimethyl)pentyl and R^{10} is hydrogen, (e) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is *n*-pentyl and R^{10} is methyl, (g) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, R^9 is isopropyl and R^{10} is methyl, (h) R^1 is methyl, R^2 is methyl, R^8 is hydroxy, ethoxy or NH_2, R^9 is cyclobutyl and R^{10} is methyl and (i) $R^1$is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, R^9 is cyclobutyl and R^{10} is methyl; and pharmaceutically acceptable salts of said compounds.

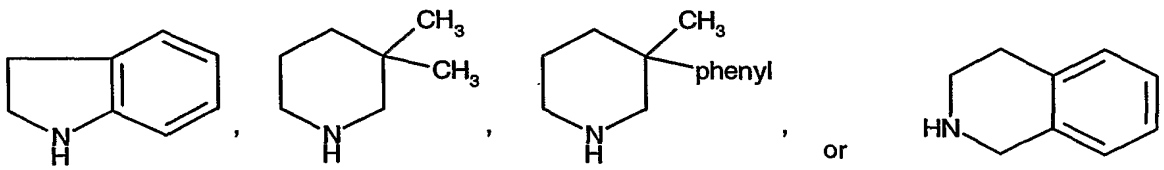
Another preferred group of compounds and pharmaceutically acceptable salts of such compounds, designated the L Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is -C(O)NR^9R^{10}, and R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_7$, $N(CH_2)_6$, $N(CH_2)_5$, $N(CH_2)_4$, morpholine,



A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the M Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $-CH_2NR^9R^{10}$, and R^{10} is hydrogen, methyl or $-COCH_3$.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the M Group, designated the N group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is methyl, *n*-propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, exo-2-norbornyl, $-CH_2$-4-fluorophenyl, $-CH_2$-4-chlorophenyl, $-CH_2$-4-isopropylphenyl, $-CH_2$-3,4-methylenedioxyphenyl, (R)-1-(1-naphthyl)ethyl, (R)-1-phenylethyl, (S)-1-phenylethyl, (R)-1-cyclohexylethyl, 1-(1,2,3,4-tetrahydronaphthyl), 1-indanyl or $-CH_2$-(1-naphthyl).

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the M Group, designated the O group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_6$, morpholine,



A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the P Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $-NHCOR^9$.

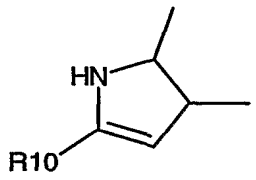
A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the P Group, designated the Q Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is cyclopropyl or cyclobutyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the R Group, contains those compounds of Formula

I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is $-S(O)_2R^{12}$, and R^{12} is 4-chlorophenyl, phenyl, 1-naphthyl, 2-naphthyl, CH_2-cyclopropyl, isopropyl, CH_2-cyclobutyl, CH_2-cyclohexyl, cyclopentyl, CH_2-4-fluorophenyl, 4-tolyl, methyl, ethyl, *n*-butyl, CH_2-phenyl or *n*-propyl.

Particularly preferred compounds of the R Group are compounds wherein (a) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, and R^{12} is ethyl, (b) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy and R^{12} is $-CH_2$-cyclobutyl, (c) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy and R^{12} is -CH2-cyclohexyl, (d) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy and R^{12} is cyclopentyl, (e) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, and R^{12} is $-CH_2$-cyclopropyl, (f) R^1 is chloro, R^2 is chloro, R^8 is hydroxy or ethoxy, and R^{12} is $-CH_2$-cyclobutyl, and (g) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, and R^{12} is $-CH_2$-cyclopropyl; and pharmaceutically acceptable salts of said compounds.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the B Group, designated the S Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each independently methyl, bromo or chloro, R^3 is hydrogen, R^4 and R^5 are taken together to form



,

R^6 is hydrogen, R^7 is hydrogen, R^8 is ethoxy, hydroxy or NH_2, and R^{10} is hydrogen or methyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the T Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 is hydrogen, and R^4 is $-OR^{11}$.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the T Group, designated the U Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^{11} is phenyl, 4-chlorophenyl or 4-fluorophenyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the V Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 is hydrogen, and R^4 is -(C_{1-6} alkyl)-OR^{11}. Particularly preferred compounds of the V Group are compounds wherein R^4 is -CH_2-OR^{11}.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the V Group, designated the W Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^{11} is phenyl or 4-fluorophenyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the D Group, designated the X Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 and R^4 are taken together to form a carbocyclic ring A of the formula -$(CH_2)_b$- or a heterocyclic ring A selected from the group consisting of -Q-$(CH_2)_c$ and -$(CH_2)_j$-Q-$(CH_2)_k$- wherein Q is O, S or NR^{17}, wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C_{1-4} alkyl, halide or oxo.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the X Group, designated the Y Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 and R^4 are taken together to form said carbocyclic ring A.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the Y Group, designated the Z Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^3 and R^4 are taken together to form -$(CH_2)_3$-, -CH_2-$C(CH_3)_2$-CH_2- or -$(CH_2)_4$-.

Particularly preferred compounds of the Z Group are compounds wherein (a) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, and R^3 and R^4 are taken together to form -$(CH_2)_3$-, (b) R^1 is chloro, R^2 is methyl, R^8 is hydroxy or ethoxy, and R^3 and R^4 are taken together to form -$(CH_2)_3$- and (c) R^1 is methyl, R^2 is methyl, R^8 is hydroxy or ethoxy, and R^3 and R^4 are taken together to form -$(CH_2)_4$-; and pharmaceutically acceptable salts of said compounds.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, designated the AA Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^8 is $-OR^9$.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AA Group, designated the AB Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is C_{1-12} alkyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AB Group, designated the AC Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is methyl, isopropyl or ethyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AC Group, designated the AD Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is ethyl.

A preferred group of the pharmaceutically acceptable salts of the compounds of Formula I, and the prodrugs, geometric and optical isomers thereof, contains those pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers wherein the salt is a potassium or a sodium salt.

A preferred group of compounds of Formula I, designated the AE Group, includes the specific compounds:

N-[3-chloro-4-(3-cyclopropylsulfamoyl-4-hydroxy-phenoxy)-5-methyl-phenyl]- oxamic acid,

N-[4-(3-cyclopropylsulfamoyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-{4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-oxamic acid,

N-{3-chloro-4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-5-methyl-phenyl}-oxamic acid,

N-[4-(7-hydroxy-indan-4-yloxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-(3,5-dichloro-4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-phenyl}-oxamic acid,

N-[3,5-dichloro-4-(3-cyclopentanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid,

N-[3,5-dichloro-4-(3-cyclopropylmethanesulfonyl-4-hydroxy-phenoxy)- phenyl]-oxamic acid,

N-[3,5-dichloro-4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)- phenyl]-oxamic acid,

N-[4-(3-cyclopropylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[3-chloro-4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid,

N-[4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl- phenyl]-oxamic acid,

N-[4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[3-chloro-4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid,

N-[3,5-dichloro-4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)- phenyl]-oxamic acid,

N-[4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl- phenyl]-oxamic acid,

N-[3-chloro-4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid,

N-[3,5-dichloro-4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)- phenyl]-oxamic acid,

N-[3,5-dichloro-4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy)- phenyl]-oxamic acid,

N-{4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl- phenyl}-oxamic acid,

N-{3-chloro-4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-5-methyl-phenyl}-oxamic acid, and the prodrugs and geometric and optical isomers thereof, and the pharmaceutically acceptable salts of the compounds, prodrugs and isomers.

A preferred group of the pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers of the AE Group, designated the AF Group, contains those pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers wherein the salt is a potassium or a sodium salt.

A preferred group of the compounds, and geometric and optical isomers thereof, of the compounds of the AE group, designated the AG Group, contains the ethyl esters of those compounds.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the B Group, designated the AH Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^5 is fluoro.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AH Group, designated the AI Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^4 is hydrogen, fluoro, chloro, methyl or cyclobutyl-methyl-carbamoyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AI Group, designated the AJ Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each independently methyl or chloro.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AJ Group, designated the AK Group, contains those compounds of

Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each methyl.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AJ Group, designated the AL Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^1 and R^2 are each chloro.

A preferred group of compounds and pharmaceutically acceptable salts of such compounds, of the AJ Group, designated the AM Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^7 is hydrogen, and R^8 is hydrogen or $-OR^9$.

A preferred group of compounds and pharmaceutical acceptable salts of such compounds, of the AM Group, designated the AN Group, contains those compounds of Formula I and pharmaceutically acceptable salts of such compounds, as shown above, wherein R^9 is methyl or ethyl.

A preferred group of compounds of Formula I, designated the AO Group, includes the specific compounds:

N-[4-(4-Fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[3,5-Dichloro-4-(4-fluoro-phenoxy)-phenyl]-oxamic acid,

N-[3,5-Dichloro-4-(3,4-difluoro-phenoxy)-phenyl]-oxamic acid,

N-[4-(3-Methyl-4-Fluoro-phenoxy)-3,5-dichloro-phenyl]-oxamic acid,

N-[3,5-Dichloro-4-(3-chloro-4-fluoro-phenoxy)-phenyl]-oxamic acid,

N-[4-(3,4-Difluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[4-(3-Chloro-4-fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[4-(3-Methyl-4-fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[3,5-Dichloro-4-(4-fluoro-phenoxy)-phenyl]-oxamic acid,

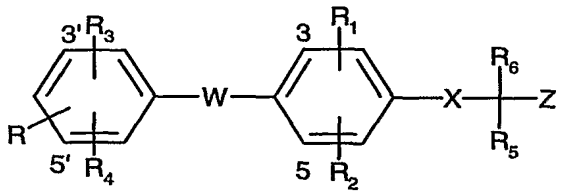
N-[3,5-Dichloro-4-(3,4-difluoro-phenoxy)-phenyl]-oxamic acid,

N-{4-[3-(Cyclobutyl-methyl-carbamoyl)-4-fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid;

N-[4-(4-Fluoro-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid, and the prodrugs and geometric and optical isomers thereof, and the pharmaceutically acceptable salts of the compounds, prodrugs and isomers.

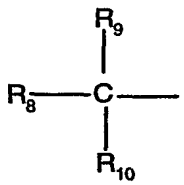
A preferred group of the pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers of the AO Group, designated the AP Group, contains those pharmaceutically acceptable salts of the compounds, prodrugs, and geometric and optical isomers wherein the salt is a potassium or a sodium salt.

A preferred group of the compounds, and geometric and optical isomers thereof, of the compounds of the AO group, designated the AQ Group, contains the ethyl esters of those compounds.



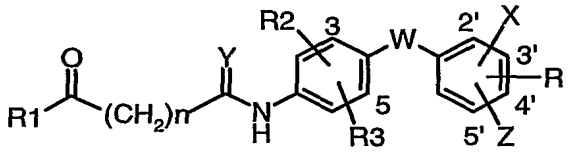
Also preferred are those compounds disclosed in EP 580 550 and U. S. Patent No. 5,569,674 and 5,654,468 of the formula

wherein R is hydroxy, esterified hydroxy or etherified hydroxy;
R_1 is halogen, trifluoromethyl or lower alkyl;
R_2 is halogen, trifluoromethyl or lower alkyl;
R_3 is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or
R_3 is the radical



wherein R_8 is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R_9 is hydroxy or acyloxy; R_{10} represents hydrogen or lower alkyl; or R_9 and R_{10} together represent oxo;
R_4 is hydrogen, halogen, trifluoromethyl or lower alkyl;
X is --NR_7 ;
W is O or S;
R_5 and R_6 together represent oxo;
R_7 represents hydrogen or lower alkyl;
Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; or a pharmaceutically acceptable salt thereof.

Even more preferred are thyromimetic compounds disclosed in WO 00/58279 incorporated herein by reference as if set forth in its entirety. Those compounds have the formula I



(I)

in which

W is O, S, S(O) or $S(O)_2$;

X is -SR4, -S(O)R4, -$S(O)_2$R4, or -$S(O)_2$NR5R6; or X is -C(O)NR5R6 provided that -C(O)NR5R6 is located at the 3'-, 4'- or 5'-position;

Y is O or H_2;

Z is hydrogen, halogen, hydroxy, optionally substituted alkoxy, aralkoxy, acyloxy or alkoxycarbonyloxy;

R is hydrogen, halogen, trifluoromethyl, lower alkyl or cycloalkyl;

R1 is hydroxy, optionally substituted alkoxy, aryloxy, heteroaryloxy, aralkoxy, cycloalkoxy, heteroaralkoxy or -NR5R6;

R2 is hydrogen, halogen or alkyl;

R3 is halogen or alkyl;

R4 is optionally substituted alkyl, aryl, aralkyl, heteroaralkyl or heteroaryl;

R5, R6 and R7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R5 and R6 combined are alkylene optionally interrupted by O, S, S(O), $S(O)_2$ or NR7 which together with the nitrogen atom to which they are attached form a 5- to 7- membered ring;

n represents zero or an integer from 1 to 4; and pharmaceutically acceptable salts thereof.

Listed below are definitions of various terms used to describe the thyromimetic compounds of the present invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances either individually or as part of a larger group).

The term "optionally substituted alkyl" refers to unsubstituted or substituted straight or branched chain hydrocarbon groups having 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, *t*-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpenthyl, octyl and the like. Substituted alkyl groups include, but are not limited to, alkyl groups substituted by one or more (e.g. two or three) of the following groups: halo, lower alkenyl, hydroxy, cycloalkyl, alkanoyl, alkoxy, alkyloxyalkoxy, alkanoyloxy, amino, alkylamino, dialkylamino, dialkylaminocarbonyl, alkanoylamino, thiol, alkylthio, alkylthiono, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, sulfonamido, nitro, cyano, carboxy, alkoxycarbonyl, aryl, aralkyl, aralkoxy, guanidino, heterocyclyl including indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl, piperidyl, morpholinyl and the like. Preferred substituents of substituted alkyl, especially of substituted alkyl of variable R1 being substituted alkoxy, are lower alkyl, cycloalkyl, lower alkenyl, benzyl, mono or disubstituted lower alkyl, e.g. ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl, □-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl, such as pivaloyloxy-methyl.

The term "lower alkyl" refers to those alkyl groups as described above having 1 to 7, preferably 1 to 4 carbon atoms.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "alkenyl" refers to any of the above alkyl groups having at least 2 carbon atoms and further containing at least one carbon to carbon double bond. Groups having two to four carbon atoms are preferred.

The term "alkylene" refers to a straight chain bridge of 1 to 6 carbon atoms connected by single bonds (e.g., $-(CH_2)_X-$ wherein x is 1 to 6), which may be substituted with 1 to 3 lower alkyl groups.

The term "cycloalkyl" refers to cyclic hydrocarbon groups of 3 to 8 carbon atoms.

The term "alkoxy" refers to alkyl-O-.

The term "acyl" refers to alkanoyl, aroyl, heteroaroyl, arylalkanoyl or heteroarylalkanoyl.

The term "alkanoyl" refers to alkyl-C(O)-.

The term "alkanoyloxy" refers to alkyl-C(O)-O-.

The terms "alkylamino" and "dialkylamino" refer to (alkyl)NH- and $(alkyl)_2N-$, respectively.

The term "alkanoylamino" refers to alkyl-C(O)-NH-.

The term "alkylthio" refers to alkyl-S-.

The term "alkylthiono" refers to alkyl-S(O)-.

The term "alkylsulfonyl" refers to alkyl-$S(O)_2$-.

The term "alkoxycarbonyl" refers to alkyl-O-C(O)-.

The term "alkoxycarbonyloxy" refers to alkyl-O-C(O)O-.

The term "alkyl" as referred to in the above definitions relates to optionally substituted alkyl as defined above.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, naphthyl, tetrahydronaphthyl, and biphenyl groups, each of which may optionally be substituted by one to four substituents

such as alkyl, halo, hydroxy, alkoxy, alkanoyl, alkanoyloxy, amino, alkylamino, dialkylamino, alkanoyl-amino, thiol, alkylthio, nitro, cyano, carboxy, carboxyalkyl, alkoxycarbonyl, alkyl-thiono, alkyl-sulfonyl, sulfonamido, heterocyclyl and the like.

The term "monocyclic aryl" refers to optionally substituted phenyl as described under aryl.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "aralkoxy" refers to an aryl group bonded through an alkoxy group.

The term "arylsulfonyl" refers to aryl-$S(O)_2$-.

The term "aroyl" refers to aryl-C(O)-.

The term "heterocyclyl" refers to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The heterocyclic group may be attached at a heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, 2-pyridone, N-lower alkyl-pyridone, e.g. N-lower alkyl-2-pyridone, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, S-oxo-thiamorpholinyl S,S-dioxo-thiamorpholinyl, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like.

Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl,

quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]-pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl) and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, benzindolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "heterocyclyl" includes substituted heterocyclic groups. Substituted heterocyclic groups refer to heterocyclic groups substituted with 1, 2 or 3 of the following:

(a) alkyl;

(b) hydroxy (or protected hydroxy);

(c) halo;

(d) oxo (i.e. = O);

(e) amino, alkylamino or dialkylamino;

(f) alkoxy;

(g) cycloalkyl;

(h) carboxy;

(i) heterocyclooxy;

(j) alkoxycarbonyl, such as unsubstituted lower alkoxycarbonyl;

(k) mercapto;

(l) nitro;

(m) cyano;

(n) sulfonamido, sulfonamidoalkyl or sulfonamidodialkyl;

(o) aryl;

(p) alkylcarbonyloxy;

(q) arylcarbonyloxy;

(r) arylthio;

(s) aryloxy;

(t) alkylthio;

(u) formyl;

(v) aralkyl; or

(w) aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkylamino, dialkylamino or halo.

The term "heterocyclooxy" denotes a heterocyclic group bonded through an oxygen bridge.

The term "heteroaryl" refers to an aromatic heterocycle, for example monocyclic or bicyclic aryl, such as pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thienyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuryl, and the like, optionally substituted by one or more substituents as described in connection with substituted aryl, e.g. by lower alkyl, lower alkoxy or halo.

The term "heteraryloxy" refers to heteroaryl-O-.

The term "heteroarylsulfonyl" refers to heteroaryl-$S(O)_2$-.

The term "heteroaroyl" refers to heteroaryl-C(O)-.

The term "heteroaralkyl" refer to a heteroaryl group bonded through an alkyl group.

Encompassed by the invention are prodrug derivatives, e.g., any pharmaceutically acceptable prodrug ester derivatives of the carboxylic acids of the invention (COR1 being carboxy) which are convertible by solvolysis or under physiological conditions to the free carboxylic acids.

Examples of such carboxylic acid esters include esters defined by COR_1, and are preferably lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono or disubstituted lower alkyl esters, e.g. the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the □-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxy-methyl ester, and the like conventionally used in the art.

Preferred meanings of R are hydrogen or lower alkyl;

Preferred meanings of R1 are hydroxy, lower alkoxy or aryloxy.

Preferred meanings of R2 are hydrogen, halogen or lower alkyl.

Preferred meanings of R3 are halogen or lower alkyl.

Preferred meanings of R4 are phenyl or phenyl substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and trifluoromethyl.

Preferred meaning of R5 is hydrogen.

Preferred meanings of R6 are phenyl or phenyl substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and trifluoromethyl.

Preferred W is O.

Preferred X is $-S(O)_2R4$ or $-S(O)_2NR5R6$

Preferred Y is O.

Preferred Z is hydrogen or hydroxy.

The integer "n" preferably is zero, 1 or 2.

The thyromimetic compounds of the invention depending on the nature of the substituents, may possess one or more asymmetric centers. The resulting diastereoisomers, enantiomers and geometric isomers are encompassed by the instant invention.

Preferred are the compounds of formula I as defined above with the proviso that when X is -C(O)NR5R6, Z is different from hydrogen.

Preferred are the compounds of formula I in which

W is O or S;

X is $-S(O)_2R4$; R4 being lower alkyl, phenyl or phenyl substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and trifluoromethyl; or is $-S(O)_2NR5R6$ or is -C(O)NR5R6; R5, in each case, being hydrogen or lower alkyl and R6, in each case, being hydrogen, lower alkyl, lower alkyl substituted by NR5R6, 3- to 7-membered cycloalkyl, phenyl, phenyl substituted by one or more substituents selected from the group consisting of lower alkyl, lower alkoxy, halogen and trifluoromethyl; pyridyl or N-lower alkyl-2-pyridone; or R5 and R6 combined, in each case, being alkylene or alkylene interrupted by O or $S(O)_2$ which together with the nitrogen atom to which they are attached form a 5- to 7- membered ring;

Y is O or H_2;

Z is hydrogen or hydroxy;

R is hydrogen;

R1 is hydroxy, lower alkoxy or NR5R6; R5 being hydrogen or lower alkyl and R6 being hydrogen, lower alkyl, lower alkoxy or R5 and R6 combined being alkylene or alkylene interrupted by O which together with the nitrogen atom to which they are attached form a 5- to 7- membered ring ;

R2 is hydrogen, halogen or lower alkyl;

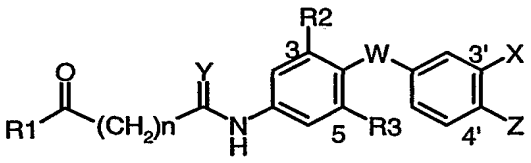
R3 is halogen or lower alkyl;

n represents zero, 1 or 2;

with the proviso that when X is -C(O)NR5R6, Z is hydroxy;

and pharmaceutically acceptable salts thereof.

Preferred are the compounds of formula IA



(IA)

in which

W is O or S;

X is -SR4, -S(O)R4, -$S(O)_2$R4, -$S(O)_2$NR5R6 or -C(O)NR5R6;

Y is O or H_2;

Z is hydrogen, halogen, hydroxy, alkoxy, aralkoxy, acyloxy or alkoxycarbonyloxy;

R1 is hydroxy, lower alkoxy or aryloxy;

R2 is hydrogen, halogen or lower alkyl;

R3 is halogen or lower alkyl;

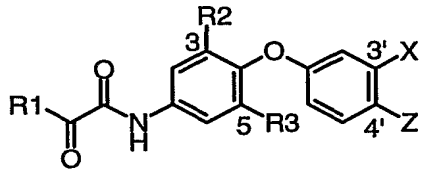
R4 is optionally substituted alkyl, aryl, aralkyl, heteroaryl or heteroaralkyl;

R5, R6 and R7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R5 and R6 combined are alkylene optionally interrupted by O, S, S(O), $S(O)_2$ or NR7 which together with the nitrogen atom to which they are attached form a 5- to 7- membered ring;

n represents zero, 1 or 2;

and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula IB



(IB)

in which

X is $-S(O)_2R4$, $-S(O)_2NR5R6$ or $-C(O)NR5R6$;

Z is hydroxy, lower alkanoyloxy or lower alkoxy;

R1 is hydroxy or lower alkoxy;

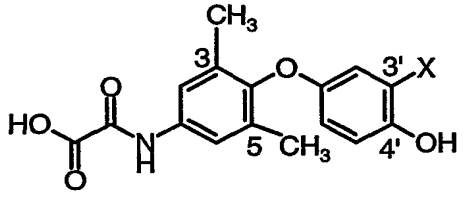
R2 and R3 are lower alkyl;

R4 is aryl;

R5, R6 and R7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R5 and R6 combined are alkylene optionally interrupted by O, S, S(O), $S(O)_2$ or NR7 which together with the nitrogen atom to which they are attached form a 5- to 7- membered ring; and pharmaceutically acceptable salts thereof.

Preferred are compounds of formula I, IA and IB, and pharmaceutically acceptable salts thereof, wherein X is $-S(O)_2R4$ or $-S(O)_2$ NR5R6.

Also preferred are the compounds of formula IC



(IC)

in which

X is $-S(O)_2R4$ or $-S(O)_2NR5R6$;

R4 is monocyclic aryl;

R5, R6 and R7 are independently hydrogen, optionally substituted alkyl or aryl; or R5 and R6 combined are CH_2CH_2-Q-CH_2CH_2 wherein Q is CH_2, O, NR7, S, S(O) or $S(O)_2$ which together with the nitrogen atom to which they are attached from a 6-membered ring; pharmaceutically acceptable prodrug esters thereof; and pharmaceutically acceptable salts thereof.

Particularly preferred are the compounds of formula IC wherein X is $S(O)_2R4$ and R4 is phenyl optionally substituted by lower alkyl, halo, lower alkoxy or trifluoromethyl; pharmaceutically acceptable salts thereof; and prodrug derivatives thereof. Most preferred is the compound N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid.

Pharmaceutically acceptable salts of any acidic compounds of the invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts, such as sodium, lithium, potassium, calcium, magnesium, as well as ammonium salts, such as ammonium, trimethylammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts.

The compounds described above may be prepared and administered in accordance with the methods set forth in WO 00/58279.

Similarly acid addition salts, such as of mineral acids, organic carboxylic, and organic sulfonic acids e.g. hydrochloric acid, methanesulfonic acid, maleic acid, are possible provided a basic group, such as pyridyl, constitutes part of the structure.

The other active component of the combinations of this invention is a statin. The term "statin", where used in the specification and the appendant claims, is synonymous with the terms "3-hydroxy-3-methylglutaryl-Coenzyme A reductase inhibitor" and "HMG-CoA reductase inhibitor." These three terms are used interchangeably throughout the specification and appendant claims. As the synonyms suggest, statins are inhibitors of 3-hydroxy-3-methylglutaryl Coenzyme A reductase and, as such, are effective in lowering the level of blood plasma cholesterol. Statins and pharmaceutically acceptable salts thereof are particularly useful in lowering low-density lipoprotein cholesterol (LDL-C) levels in mammals, and particularly in humans.

The HMG-CoA reductase inhibitors suitable for use herein include, but are not limited to, pitavastatin, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, cerivastatin,

velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, rosuvastatin, or lovastatin; or a pharmaceutically acceptable salt of pitavastatin, simvastatin, pravastatin, rivastatin, cerivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, rosuvastatin and lovastatin. However, it is to be noted that simvastatin is a preferred statin and pitavastatin is the particularly preferred statin to be employed in the present combination.

The statins disclosed herein are prepared by methods well-known to those skilled in the art. Specifically, pitavastatin may be prepared according to the method disclosed in EP 0 520 406, which is incorporated herein by reference. Simvastatin may be prepared according to the method disclosed in U.S. Patent 4,444,784, which is incorporated herein by reference. Pravastatin may be prepared according to the method disclosed in U.S. Patent 4,346,227, which is incorporated herein by reference. Cerivastatin may be prepared according to the method disclosed in U.S. Patent 5,502,199, which is incorporated herein by reference. Cerivastatin may alternatively be prepared according to the method disclosed in European Patent Application Publication No. EP617019. Mevastatin may be prepared according to the method disclosed in U.S. Patent 3,983,140, which is incorporated herein by reference. Velostatin may be prepared according to the methods disclosed in U.S. Patent 4,448,784 and U.S. Patent 4,450,171, both of which are incorporated herein by reference. Fluvastatin may be prepared according to the method disclosed in U.S. Patent 4,739,073, which is incorporated herein by reference. Compactin may be prepared according to the method disclosed in U.S. Patent 4,804,770, which is incorporated herein by reference. Rosuvastatin may be prepared acording to the method disclosed in EP 0 521 471. Lovastatin may be prepared according to the method disclosed in U.S. Patent 4,231,938, which is incorporated herein by reference. Dalvastatin maybe prepared according to the method disclosed in European Patent Application Publication No. 738510 A2. Fluindostatin may be prepared according to the method disclosed in European Patent Application Publication No. 363934 Al. Dihydrocompactin may be prepared according to the method disclosed in U.S. Patent 4,450,171, which is incorporated herein by reference.

It will be recognized that certain of the above statins contain either a free carboxylic acid or a free amine group as part of the chemical structure. Further, certain statins within the scope of this invention contain lactone moieties, which exist in equilibrium with the free carboxylic acid form. These lactones can be maintained as carboxylates by preparing pharmaceutically acceptable salts of the lactone. Thus, this invention includes

pharmaceutically acceptable salts of those carboxylic acids or amine groups. The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g., sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically acceptable add addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

The pharmaceutically acceptable cationic salts of statins containing free carboxylic acids may be readily prepared by reacting the free acid form of the statin with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine, and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (sodium or potassium ethylhexanoate, magnesium oleate), employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The pharmaceutically acceptable acid addition salts of statins containing free amine groups may be readily prepared by reacting the free base form of the statin with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate), or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed.

However, when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate, or the phosphate are desired, the appropriate and exact chemical equivalents of acid will

generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

Further, the statins of the instant invention and the pharmaceutically acceptable salts of the statins of the instant invention may also occur as hydrates or solvates. Said hydrates and solvates are also within the scope of the invention.

The same holds true for the thyromimetic compounds of the present invention.

In yet another aspect of the present invention there are provided pharmaceutical compositions comprising a thyromimetic compound, a statin and a pharmaceutically acceptable carrier. Preferably the thyromimetic compound is N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid and the statin is pitavastatin, fluvastatin or simvastatin.

1. Administration

The pharmaceutical composition according to the present invention comprises a "kit of parts" in the sense that the components can be dosed independently or by use of different fixed combinations with distinguished amounts of the components at different time points. The parts of the "kit of parts" can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the "kit of parts". Preferably, the time intervals are chosen such that the effect on the treated disease or condition in the combined use of the parts is larger than the effect that would be obtained by use of only any one of the components.

The invention relates in particular to a commercial package comprising jointly therapeutically effective amounts of a thyromimetic agent, in free or pharmaceutically acceptable salt form, and a statin, in free form or in form of a pharmaceutically acceptable salt thereof together with instructions for use thereof in the treatment of conditions associated with elevated Lp(a) levels.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals,

including man, for the treatment of diseases associated with an elevated level of Lp(a), such as CHD, ischaemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, reduction in necrosis after myocardial infarction, dyslipidemia and post-prandial lipemia, comprising administering a therapeutically effective amount of a combination of compounds of the invention, alone or in combination with one or more pharmaceutically acceptable carriers.

Any suitable route of administration may be employed for providing a mammal with a therapeutically effective amount of the pharmaceutical combinations and compositions of the present invention. For example, oral, rectal, vaginal, topical, parental (subcutaneous, intramuscular, intravenous, transdermal) and like forms of administration may be employed. Dosage formulations include ointments, foams, gels, transdermal patches, tablets (both fractionable and non-fractionable), caplets, powders for inhalations, gelcaps, capsules , elixirs, syrups, chewable tablets, lozenges, troches, dispersions, aerosols, solutions, fast-dissolving wafers, suppositories or suspensions or other known and effective delivery methods.

In addition to the dosage formulations set out above, the pharmaceutical combinations and compositions of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U. S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719 and by "fast-melt" means which include delivery devices which rapidly dissolve in the mouth. Rapid dissolution is meant to include dissolution which takes place in the patient's mouth within less than three minutes. Delivery devices for this type of formulation include, but are not limited to, tablets and capsules. An example of a fast-melt means as used herein is described in U. S. Patent No. 5,178,878 which discloses an effervescent dosage form with microparticles for rapid dissolution of the tablet or capsule.

Oral dosing is preferred. In preparing the compositions in oral dose form, any of the usual pharmaceutical carriers may be employed including any material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material involved in carrying, formulating or transporting a chemical agent. Specific examples are water, glycols, oils, alcohols and the like in the case of oral liquid preparations. In oral solid forms solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like may be employed. Oral solid preparations are preferred over the oral

liquid preparations. A preferred oral solid preparation is capsules and tablets, because of their ease of administration.

For parental compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises PEG, saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect on the skin. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient(s) calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

Suitable formulations for transdermal application include an effective amount of a combination of compounds of the invention with carrier. Advantageous carriers include absorbable pharmaco-logically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compounds to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

The method of administration will be determined by the attendant physician or other person skilled in the art after an evaluation of the subject's condition and requirements.

Methods of preparing various pharmaceutical compositions with a certain amount of active compounds are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see Remington 's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pennsylvania, 15th Edition (1975).

The pharmaceutical combinations and compositions of the present invention may be administered in fixed and non-fixed combinations.

The therapeutically effective dosage of the pharmaceutical compositions of this invention will vary with the severity of the condition to be treated, and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, medical history of the patient, the presence of diseases and response of the individual patient.

In general, in accordance with this invention, the thyromimetic compound is generally administered in a dosage of about 1 μg to about 50 mg. Preferably, the thyromimetic compounds are administered in a dosage of about 1 μg to about 5 mg, even more preferably from about 5 μg to about 50 μg, more preferably from about 5 μg to about 10 μg, with the optimum dose being 5 μg. The dosage of active compounds is also dependent on the species of warm-blooded animal (mammal), on the form of administration, and on the compound involved.

In general, in accordance with this invention, the above statins are administered in the following dosage amounts:

Pitavastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg;

Simvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg;

Pravastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg;

Cerivastatin, generally about 25 clog to about 5 mg and preferably about 1 mg to about 3.2 mg;

Fluvastatin, generally about 2.5 mg to about 160 mg and preferably about 20 mg to about 80 mg;

Rosuvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg;

Lovastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 80 mg; and

Atorvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 80 mg.

It will be recognized by a skilled person that the free base form or other salt forms of the above thyromimetic and statin compounds may be used in this invention. Calculation of the dosage amount for these other forms of or the free base form or other salt forms of the statins is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

The dosage amounts are administered, based upon the molecular weights of the compounds, in a ratio of statin:thyromimetic ranging from between 160:1 to 8:1, preferably about 40:1.**EXAMPLES**

The present invention is further described by the following examples. The examples are provided solely to illustrate the invention by reference to specific embodiments. These exemplification's, while illustrating certain specific aspects of the invention, do not portray the limitations or circumscribe the scope of the disclosed invention.

Example 1

Evaluation of the effects of N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid and Fluvastatin as a combined therapy on the lipid profile of non-human primates

Animals

Adult male cynomolgus monkeys (*Macaca fascicularis*) weighing 6-12 kg were fed a standard monkey chow diet supplemented with fresh fruits and vegetables. Purified water was provided *ad libitum.* Monkeys were maintained on a 12-hour light/dark cycle. Each animal served as its own control and each dosing regime was followed by a wash out period.

Experimental protocol

Animals were dosed orally once a day with either N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid at 75 ug/kg, fluvastatin at 30 mg/kg or a combination of fluvastatin (30 mg/kg) and N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid (75 ug/kg) for a period of 3 weeks. Blood samples were obtained after an overnight fast at the beginning of the study (baseline) and after the 1st, 2nd and 3rd week of treatment.

Blood collection and biochemical analyses

Blood samples were collected into Vacutainer tubes from the femoral vein of restrained non-sedated animals. Blood was centrifuged at 2,000 rpm for 20 min at 4°C. Plasma samples

were divided into aliquots and stored at –70°C for the measurement of Lp(a) whereas all the other lipid parameters were analyzed in fresh plasma.

Plasma concentrations of total cholesterol (TC) and triglycerides (TG) were determined by enzymatic methods using commercial kits (Sigma Diagnostics). High-density lipoprotein cholesterol (HDL-C) concentration was measured after precipitation of apoB-containing lipoproteins. Low-density lipoprotein cholesterol (LDL-C) concentration was calculated by subtracting HDL-C from TC.

Plasma concentrations of Lp(a) were determined by a commercial Lp(a) ELISA (Sigma Diagnostics). Samples from each study were assayed in a single run.

Illustrative of the invention, the thyromimetic compound N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid in combination with fluvastatin lowered the levels of Lp(a) to a level below that achieved by administration of N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid alone. Lp(a) levels were significantly and synergistically lowered. "Synergistically" is meant to include a level which is between about 50 and about 150% lower for the combination as compared to the thyromimetic agent alone.

Although the present invention has been described in considerable detail with reference to certain preferred versions thereof, other versions are possible without departing from the spirit and scope of the preferred versions contained herein. All references and Patents (U.S. and others) referred to herein are hereby incorporated by reference in their entirety as if set forth in full herein.

WHAT IS CLAIMED IS:

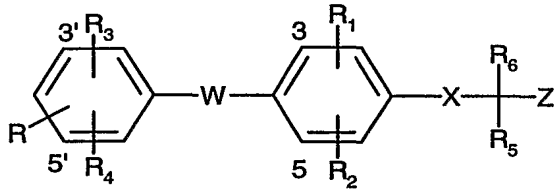
1. The use of a combination comprising a thyromimetic compound and a statin for the manufacture of a medicament for lowering Lp(a) levels.

2. The use of a combination comprising a thyromimetic compound and a statin for the manufacture of a medicament for the treatment of a condition associated with elevated levels of Lp(a).

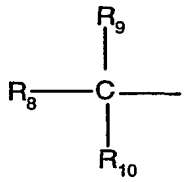
3. Use according to claim 1 or 2 for the manufacture of a medicament for the treatment of a condition that is selected from the group consisting of coronary heart disease, ischaemic stroke, restenosis after angioplasty, peripheral vascular disease, intermittent claudication, reduction in necrosis after myocardial infarction, dyslipidemia and post-prandial lipemia.

4. Use according to claim 2 for the manufacture of a medicament for the treatment of dyslipidemia.

5. Use according to any one of claims 1 to 4, wherein the thyromimetic compound is a compound of formula



wherein R is hydroxy, esterified hydroxy or etherified hydroxy;
R_1 is halogen, trifluoromethyl or lower alkyl;
R_2 is halogen, trifluoromethyl or lower alkyl;
R_3 is halogen, trifluoromethyl, lower alkyl, aryl, aryl-lower alkyl, cycloalkyl or cycloalkyl-lower alkyl; or
R_3 is the radical



wherein R_8 is hydrogen, lower alkyl, aryl, cycloalkyl, aryl-lower alkyl or cycloalkyl-lower alkyl; R_9 is hydroxy or acyloxy; R_{10} represents hydrogen or lower alkyl; or R_9 and R_{10} together represent oxo;

R_4 is hydrogen, halogen, trifluoromethyl or lower alkyl;

X is --NR_7 ;

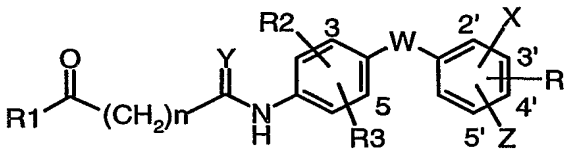
W is O or S;

R_5 and R_6 together represent oxo;

R_7 represents hydrogen or lower alkyl;

Z represents carboxyl, carboxyl derivatized as a pharmaceutically acceptable ester or as a pharmaceutically acceptable amide; or a pharmaceutically acceptable salt thereof.

6. Use according to any one of claims 1 to 4, wherein the thyromimetic compound is a compound of formula I



(I)

in which

W is O, S, S(O) or $S(O)_2$;

X is -SR4, -S(O)R4, -$S(O)_2$R4, or -$S(O)_2$NR5R6; or X is -C(O)NR5R6 provided that

-C(O)NR5R6 is located at the 3'-, 4'- or 5'-position;

Y is O or H_2;

Z is hydrogen, halogen, hydroxy, optionally substituted alkoxy, aralkoxy, acyloxy or alkoxycarbonyloxy;

R is hydrogen, halogen, trifluoromethyl, lower alkyl or cycloalkyl;

R1 is hydroxy, optionally substituted alkoxy, aryloxy, heteroaryloxy, aralkoxy, cycloalkoxy, heteroaralkoxy or -NR5R6;

R2 is hydrogen, halogen or alkyl;

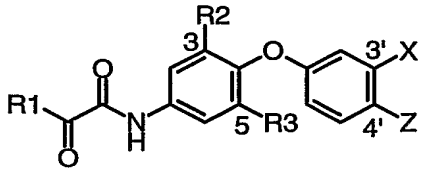
R3 is halogen or alkyl;

R4 is optionally substituted alkyl, aryl, aralkyl, heteroaralkyl or heteroaryl;

R5, R6 and R7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R5 and R6 combined are alkylene optionally interrupted by O, S, S(O), $S(O)_2$ or NR7 which together with the nitrogen atom to which they are attached form a 5- to 7- membered ring;

n represents zero or an integer from 1 to 4; and pharmaceutically acceptable salts thereof.

7. Use according to claim 6, wherein the thyromimetic compound is a compound of formula



(IB)

wherein

X is $-S(O)_2R4$, $-S(O)_2NR5R6$ or -C(O)NR5R6;

Z is hydroxy, lower alkanoyloxy or alkoxy;

R1 is hydroxy or lower alkoxy;

R2 and R3 are lower alkyl;

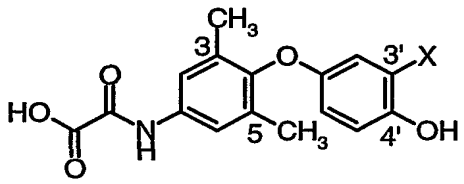
R4 is aryl;

R5, R6 and R7 are independently hydrogen, optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R5 and R6 combined are alkylene optionally

interrupted by O, S, S(O), $S(O)_2$ or NR7 which together with the nitrogen atom to which they are attached form a 5- to 7- membered ring; which may optionally contain another heteratom selected from oxygen, nitrogen and sulfur;

or a pharmaceutically acceptable salt thereof.

8. Use according to claim 6, wherein the thyromimetic compound is a compound of formula



(IC)

wherein

X is $-S(O)_2R4$ or $-S(O)_2NR5R6$;

R4 is monocyclic aryl;

R5, R6 and R7 are independently hydrogen, optionally substituted alkyl or aryl; or R5 and R6 combined are CH_2CH_2-Q-CH_2CH_2 wherein Q is CH_2, O, NR7, S, S(O) or $S(O)_2$ which together with the nitrogen atom to which they are attached from a 6-membered ring; or a pharmaceutically acceptable prodrug ester thereof; or a pharmaceutically acceptable salt thereof.

9. Use according to any one of claims 1 to 4, wherein the thyromimetic compound is selected from the group consisting of:

N-[4-(4-Hydroxy-3-phenylsulfamoylphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-[4-(4-Hydroxy-3-isopropylsulfamoylphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-[4-(4-Hydroxy-3-isobutylsulfamoylphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-{4[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[3-(2,2-Dimethylpropylsulfamoyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-[4-(4-Hydroxy-3-phenylsulfamoylphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-{4-[3-(4-Fluorophenylsulfamoyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-{3-(2-Fluorophenylsulfamoyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[3-(3-Fluorophenylsulfamoyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(4-methoxyphenylsulfamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[3-(4-Fluorobenzylsulfamoyl)-4-hydroxy-phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(methylphenylsulfamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-[4-(4-Hydroxy-3-propylsulfamoylphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-[4-(4-Hydroxy-3-isopropylsulfamoylphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-[4-(3-Butylsulfamoyl-4-hydroxyphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-[4-(4-Hydroxy-3-isobutylsulfamoylphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-[4-(3-t-Butylsulfamoyl-4-hydroxyphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-[4-(3-Cyclohexylsulfamoyl-4-hydroxyphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-[4-(3-Dimethylsulfamoyl-4-hydroxyphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-{4-[4-Hydroxy-3-(pyrrolidine-1-sulfonyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(piperidine-1-sulfonyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(2-methoxyethylsulfamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(morpholine-4-sulfonyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[3-(Dioxothiomorpholine-4-sulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(pyridin-3-ylsulfamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-ylsulfamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[3(4-Fluorophenylsulfamoyl)-4-hydroxyphenylsulfanyl]-3,5-dimethylphenyl}oxamic acid;

N-{4-[3-(4-Fluorophenylsulfamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[3-(4-Fluorophenylsulfamoyl)-4-hydroxyphenoxy]-3-methylphenyl}oxamic acid;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-[4-(3-Benzenesulfonyl-4-hydroxyphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-{4-[3-(4-Chlorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(toluene-4-sulfonyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(4-methoxybenzenesulfonyl)phenoxy]-3,5-dimethyl-phenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(4-trifluoromethylbenzenesulfonyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-[4-(4-Hydroxy-3-methanesulfonylphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-{4-[3-(Butane-1-sulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(propane-2-sulfonyl)phenoxy]-3,5-dimethylphenyl}oxamic acid

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}malonamic acid;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}succinamic acid;

3-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenylamino}propionic acid;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3-methylphenyl}oxamic acid;

N-{3,5-Dibromo-4[3-(4-fluorobenzenesulfonyl)-4-hydroxyphenoxy]phenyl}oxamic acid;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxalamide;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}-N'-propyl-oxalamide;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}-N'-isopropyl-oxalamide;

N-Butyl-N'-{4-[3-(4-fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}-oxalamide;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}-N'-(2-methoxyethyl)oxalamide;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}-2-morpholin-4-yl-2-oxoacetamide;

N-{4-[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}-2-morpholin-4-yl-2-oxoacetamide;

N-{4-[4-Hydroxy-3-(piperidine-1-carbonyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-{4-[4-Hydroxy-3-(morpholine-4-carbonyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

N-[4-(3-Cyclohexylcarbamoyl-4-hydroxyphenoxy)-3,5-dimethylphenyl]oxamic acid;

N-{4-[4-Hydroxy-3-(2-methoxyethylcarbamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

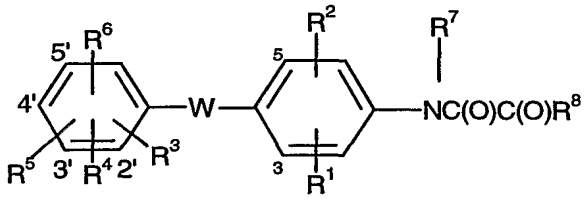
N-{4-[4-Hydroxy-3-(2-morpholin-4-yl-ethylcarbamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid; and

N-{4-[4-Hydroxy-3-(pyridin-3-ylcarbamoyl)phenoxy]-3,5-dimethylphenyl}oxamic acid;

or a pharmaceutically acceptable salt thereof.

10. Use according to any one of claims 1 to 4, wherein the thyromimetic compound is N-{4[3-(4-Fluorobenzenesulfonyl)-4-hydroxyphenoxy]-3,5-dimethylphenyl}oxamic acid; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

11. Use according to any one of claims 1 to 4, wherein the thyromimetic compound is a compound of formula



prodrugs thereof, geometric and optical isomers thereof, and pharmaceutically acceptable salts of said compounds, said prodrugs, and said isomers, wherein:

R^1, R^2 and R^3 are each independently hydrogen, halogen, C_{1-6} alkyl, trifluoromethyl, -CN, $-OCF_3$ or $-OC_{1-6}$ alkyl;

R^4 is hydrogen, C_{1-12} alkyl optionally substituted with one to three substitutents independently selected from Group Z, C_{2-12} alkenyl, halogen, -CN, aryl, heteroaryl, C_{3-10} cycloalkyl, heterocycloalkyl, $-S(O)_2NR^9R^{10}$, $-C(O)NR^9R^{10}$, $-(C_{1-6}$ alkyl)$-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$, $-(C_{1-6}$ alkyl)$-OR^{11}$, $-OR^{11}$or $-S(O)_aR^{12}$, provided that, where R^5 is not fluoro, R^4 is $-S(O)_2NR^9R^{10}$, $-C(O)NR^9R^{10}$, $-(C_{1-6}$ alkyl)$-NR^9R^{10}$, $-NR^9C(O)R^{10}$, $-NR^9C(O)NR^9R^{10}$, $-NR^9S(O)_2R^{10}$, $-(C_{1-6}$ alkyl)$-OR^{11}$, $-OR^{11}$or $-S(O)_aR^{12}$;

or R^3 and R^4 may be taken together to form a carbocyclic ring A of the formula $-(CH_2)_b-$ or a heterocyclic ring A selected from the group consisting of $-Q-(CH_2)_c-$ and $-(CH_2)_j-Q-(CH_2)_k-$ wherein Q is O, S or NR^{17}, wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C_{1-4} alkyl, halide or oxo;

R^5 is fluoro, hydroxy, C_{1-4} alkoxy or $OC(O)R^9$;

or R^4 and R^5 may be taken together to form a heterocyclic ring B selected from the group consisting of $-CR^9=CR^{10}$ -NH-, $-N=CR^9$-NH-, $-CR^9=CH$-O- and $-CR^9=CH$-S-;

R^6 is hydrogen, halogen, C_{1-4} alkyl or trifluoromethyl;

R^7 is hydrogen or C_{1-6} alkyl;

R^8 is $-OR^9$ or $-NR^{19}R^{20}$;

R^9 and R^{10} for each occurrence are independently (A) hydrogen, (B) C_{1-12} alkyl optionally substituted with one or more substituents independently selected from Group V, (C) C_{2-12} alkenyl, (D) C_{3-10} cycloalkyl optionally substituted with one or more substituents independently selected from C_{1-6} alkyl, C_{2-5} alkynyl, C_{3-10} cycloalkyl, -CN, $-NR^{13}R^{14}$, oxo, $-OR^{18}$, $-COOR^{18}$ or aryl optionally substituted with X and Y, (E) aryl optionally substituted with X and Y, or (F) het optionally substituted with X and Y;

or R^9 and R^{10} for any occurrence may be taken together to form a heterocyclic ring C optionally further containing a second heterogroup selected from the group consisting of -O-, $-NR^{13}$- and -S-, and optionally further substituted with one or more substituents independently selected from C_{1-5} alkyl, oxo, $-NR^{13}R^{14}$, $-OR^{18}$, $-C(O)_2R^{18}$, -CN, $-C(O)R^9$, aryl optionally substituted with X and Y, het optionally substituted with X and Y, C_{5-6} spirocycloalkyl, and a carbocyclic ring B selected from the group consisting of 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated carbocyclic rings, and including any bicyclic group in which said carbocyclic ring B is fused to a carbocyclic ring C selected from the group consisting of 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated carbocyclic rings;

R^{11} is C_{1-12} alkyl optionally substituted with one or more substituents independently selected from Group V, C_{2-12} alkenyl, C_{3-10} cycloalkyl, trifluoromethyl, difluoromethyl, monofluoromethyl, aryl optionally substituted with X and Y, het optionally substituted with X and Y, $-C(O)NR^9R^{10}$ or $-C(O)R^9$;

R^{12} is C_{1-12} alkyl optionally substituted with one or more substituents independently selected from Group V, C_{2-12} alkenyl, C_{3-10} cycloalkyl, aryl optionally substituted with X and Y, or het optionally substituted with X and Y;

R^{13} and R^{14} for each occurrence are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, -(C_{1-6} alkyl)-C_{1-6} alkoxy, aryl optionally substituted with X and Y, het optionally substituted with X and Y, -(C_{1-4} alkyl)-aryl optionally substituted with X and Y, -(C_{1-4} alkyl)-heterocycle

optionally substituted with X and Y, -(C_{1-4} alkyl)-hydroxy, -(C_{1-4} alkyl)-halo, -(C_{1-4} alkyl)-poly-halo, -(C_{1-4} alkyl)-$CONR^{15}R^{16}$ or C_{3-10} cycloalkyl;

R^{15} and R^{16} for each occurrence are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl or aryl optionally substituted with X and Y;

R^{17} is hydrogen, alkyl, C_{1-6} alkyl, $-COR^9$ or $-SO_2R^9$;

R^{18} is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, -(C_{1-6} alkyl)-C_{1-6} alkoxy, aryl optionally substituted with X and Y, het optionally substituted with X and Y, -(C_{1-4} alkyl)-aryl optionally substituted with X and Y, -(C_{1-4} alkyl)-heterocycle optionally substituted with X and Y, -(C_{1-4} alkyl)-hydroxy, -(C_{1-4} alkyl)-halo, -(C_{1-4} alkyl)-poly-halo, -(C_{1-4} alkyl)-$CONR^{15}R^{16}$, -(C_{1-4} alkyl)-(C_{1-4} alkoxy) or C_{3-10} cycloalkyl;

R^{19} is hydrogen or C_{1-6} alkyl;

R^{20} is hydrogen or C_{1-6} alkyl;

W is 0, $S(O)_d$, CH_2 or NR^9;

Group Z is C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-CF_3$, $-OCF_3$, hydroxy, oxo, -CN, aryl, heteroaryl, C_{3-10} cycloalkyl, heterocycloalkyl, $-S(O)_aR^{12}$, $-S(O)_2NR^9R^{10}$, $-C(O)R^9R^{10}$, and $-NR^9R^{10}$;

Group V is halogen, $-NR^{13}R^{14}$, $-OCF_3$, $-OR^9$, oxo, trifluoromethyl, -CN, C_{3-10} cycloalkyl, aryl optionally substituted with X and Y, and het optionally substituted with X and Y;

het for each occurrence is a heterocyclic ring D selected from the group consisting of 4-, 5-, 6-, 7-and 8-membered partially and fully saturated, and unsaturated, heterocyclic rings containing from one to four heteroatoms independently selected from the group consisting of N, O and S, and including any bicyclic group in which said heterocyclic ring D is fused to a benzene ring or a heterocyclic ring E selected from the group consisting of 4-, 5-, 6-, 7- and 8-membered partially and fully saturated, and unsaturated, heterocyclic rings containing from one to four heteroatoms independently selected from the group consisting of N, O and S;

X and Y for each occurrence are independently (A) hydrogen, (B) halogen, (C) trifluoromethyl, (D) $-OCF_3$, (E) -CN, (F) C_{1-6} alkyl optionally substituted with one or more

substituents independently selected from the group consisting of halogen, $-OCF_3$, $-CF_3$ and phenyl, (G) C_{1-6} alkoxy, (H) aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, $-OCF_3$, $-CF_3$, C_{1-4} alkyl and C_{1-4} alkoxy, (I) $-C(O)_2R^{13}$, (J) $-C(O)NR^{13}R^{14}$, (K) $-C(O)R^{13}$, (L) $-NR^{13}C(O)NR^{13}R^{14}$ and (M) $-NR^{13}C(O)R^{14}$; or X and Y for any occurrence in the same variable may be taken together to form (a) a carbocyclic ring D of the formula $-(CH_2)_e-$ or (b) a heterocyclic ring F selected from the group consisting of $-O(CH_2)_fO-$,$(CH_2)_gNH-$ and -CH=CHNH- ;

a and d are each independently 0, 1 or 2;

b is 3, 4, 5, 6 or 7;

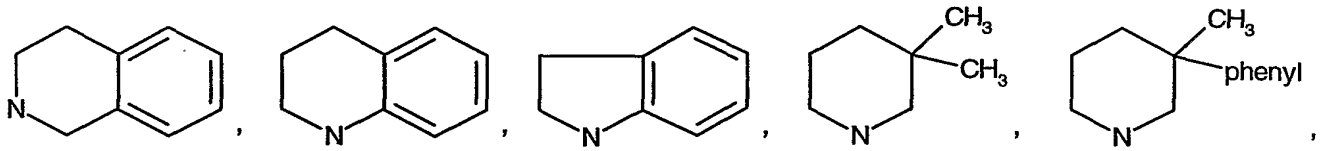
c, f, g, j and k are each independently 2, 3, 4, 5 or 6; and

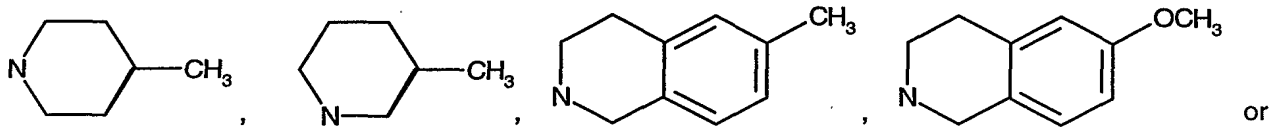
e is 3, 4, 5, 6 or 7.

12. Use according to claim 11, wherein W is oxygen and wherein R^1 is located at the 3 position, R^2 is located at the 5 position, R^3 is located at the 2' position, R^4 is located at the 3' position, R^5 is located at the 4' position and R^6 is located at the 5' position and wherein R^1 and R^2 are each independently hydrogen, C_{1-6} alkyl, bromo, or chloro, R^3 is hydrogen, R4 is $-C(O)NR^9R^{10}$, $-S(O)_2NR^9R^{10}$, or $S(O)_aR^{12}$, or R^3 and R^4 may be taken together to form a carbocyclic ring A of the formula $-(CH_2)_b-$ or a heterocyclic ring A selected from the group consisting of $-Q-(CH_2)_C-$ and $-(CH_2)_j-Q-(CH_2)_k-$ wherein Q is O, S or NR^{17}, wherein said carbocyclic ring A and said heterocyclic ring A are each independently optionally substituted with one or more substituents independently selected from C_{1-4} alkyl, halide or oxo, R^5 is fluoro or hydroxy, R^8 is hydroxy, methoxy, ethoxy, isopropoxy, NH_2, or $NH(CH_3)$, R^6 and R^7 are each hydrogen.

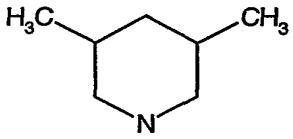
13. Use according to claim 11 or 12, wherein R^4 is $-C(O)NR^9R^{10}$ and wherein R^1 and R^2 are each independently methyl or chloro, R^5 is hydroxy, R^8 is hydroxy or ethoxy, R^9 is methyl, ethyl, isopropyl, *n*-propyl, isobutyl, *n*-butyl, *n*-pentyl, *n*-hexyl, 4-fluorophenyl, $-CH_2$-2-thienyl, cyclopropyl, $-CH_2$-cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-CH_2$-cyclohexyl, endo-2-norbornyl, exo-2-norbornyl, (S)-1-phenylethyl, (R)-1-phenylethyl, $-CH_2$-2-chlorophenyl, $-CH_2$-4-chlorophenyl, $-CH_2$-4-fluorophenyl, $-CH_2$-3-chloro-4-fluorophenyl, $-CH_2$-2-chloro-4-fluorophenyl, $-CH_2$-2-fluoro-4-chlorophenyl, $-CH_2$-3,4-difluorophenyl, $-CH_2$-4-isopropylphenyl, $-CH_2$-2,3-dichlorophenyl, $-CH_2$-2,4-dichlorophenyl, $-CH_2$-3,4-dichlorophenyl, $-CH_2$-3-trifluoromethyl-4-chlorophenyl,

4-phenylphenyl, 3-(2,4-dimethyl)pentyl, (R)-1-(1-naphthyl)ethyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, (R)-1-(2-naphthyl)ethyl, (R)-2-(1-naphthyl)ethyl, $-CH_2$-(1-naphthyl), (R)-1-cyclohexylethyl, (S)-1-cyclohexylethyl, $-CH_2$-3,4-methylenedioxyphenyl, $-CH_2$-4-*t*-butylphenyl, $-CH_2$-2,3-dichlorophenyl, 1-indanyl, (R)-1-indanyl, (S)-1-indanyl, 5-indanyl, 1-(1,2,3,4-tetrahydronaphthyl) or (R)-1-cyclohexylethyl, and ^{R10} is hydrogen, methyl, or ethyl, or R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_7$, $N(CH_2)_6$, $N(CH_2)_5$, $N(CH_2)_4$, morpholine,



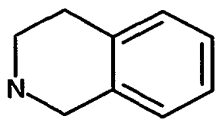


or



and wherein R^4 is $-S(O)_2NR^9R^{10}$.

14. Use according to claim 13, wherein R^1 and R^2 are each independently methyl or chloro, R^3 is hydroxy, isopropoxy, or ethoxy, R^9 is hydrogen, isopropyl, $-CH_2$-2-thienyl, $-CH_2$-cyclopropyl, cyclopropyl, $-(CH_2)_2OH$, exo-2-norbornyl, methyl, ethyl, 4-fluorophenyl, cyclobutyl, cyclopentyl, cyclohexyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-octyl or *n*-decyl, and R^{10} is hydrogen or methyl, or R^9 and R^{10} are taken together with the nitrogen atom to which they are attached to form $N(CH_2)_4$, $N(CH_2)_5$, morpholine or



and wherein R^4 is $-S(O)_aR^{12}$.

15. Use according to claim 11, wherein the compound is selected from the group consisting of:

N-[3-chloro-4-(3-cyclopropylsulfamoyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid,

N-[4-(3-cyclopropylsulfamoyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-{4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-oxamic acid,

N-{3-chloro-4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-5-ethyl-phenyl}-oxamic acid,

N-[4-(7-hydroxy-indan-4-yloxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-(3,5-dichloro-4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy- phenoxy]-phenyl}-oxamic acid,

N-[3,5-dichloro-4-(3-cyclopentanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid,

N-[3,5-dichloro-4-(3-cyclopropylmethanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid,

N-[3,5-dichloro-4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid,

N-[4-(3-cyclopropylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[3-chloro-4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid,

N-[4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[3-chloro-4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid,

N-[3,5-dichloro-4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid,

N-[4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid,

N-[3-chloro-4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid,

N-[3,5-dichloro-4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid,

N-[3,5-dichloro-4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy)-phenyl]-oxamic acid,

N-{4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-oxamic acid,

N-{3-chloro-4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-5-methyl-phenyl}-oxamic acid,

N-[3-chloro-4-(3-cyclopropylsulfamoyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid ethyl ester,

N-[4-(3-cyclopropylsulfamoyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid ethyl ester,

N-{4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-oxamic acid ethyl ester,

N-{3-chloro-4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-5-methyl-phenyl}-oxamic acid ethyl ester,

N-[4-(7-hydroxy-indan-4-yloxy)-3,5-dimethyl-phenyl]-oxamic acid ethyl ester,

N-(3,5-dichloro-4-[3-(cyclobutyl-methyl-carbamoyl)-4-hydroxy-phenoxy]-phenyl}-oxamic acid ethyl ester,

N-[3,5-dichloro-4-(3-cyclopentanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid ethyl ester,

N-[3,5-dichloro-4-(3-cyclopropylmethanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid ethyl ester,

N-[3,5-dichloro-4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid ethyl ester,

N-[4-(3-cyclopropylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid ethyl ester,

N-[3-chloro-4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid ethyl ester,

N-[4-(3-cyclobutylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid ethyl ester,

N-[4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid ethyl ester,

N-[3-chloro-4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid ethyl ester,

N-[3,5-dichloro-4-(3-cyclopentylmethanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid ethyl ester,

N-[4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)-3,5-dimethyl-phenyl]-oxamic acid ethyl ester,

N-[3-chloro-4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)-5-methyl-phenyl]-oxamic acid ethyl ester,

N-[3,5-dichloro-4-(3-cyclohexylmethanesulfonyl-4-hydroxy-phenoxy)-phenyl]-oxamic acid ethyl ester,

N-[3,5-dichloro-4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy)-phenyl]-oxamic acid ethyl ester,

N-{4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl}-oxamic acid ethyl ester, and

N-{3-chloro-4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-5-methyl-phenyl}-oxamic acid ethyl ester;

or a prodrug, isomer or pharmaceutically acceptable salt thereof.

16. Use according to any one of claims 1 to 15, wherein the statin is selected from the group consisting of atorvastatin, pitavastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, lovastatin, dalvastatin, rosuvastatin and fluindostatin or a pharmaceutically accetable salt thereof.

17. Use according to claim 16, wherein the statin is simvastatin, pitavastatin or fluvastatin.

18. Use according to any one of claims 1 to 4, comprising N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid or a pharmaceutically acceptable salt thereof and a statin selected from the group consisting of simvastatin, pitavastatin and fluvastatin or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a thyromimetic compound and a statin a compound, prodrug, isomer or pharmaceutically acceptable salt, and a pharmaceutically acceptable vehicle, diluent or carrier.

20. A composition according to claim 19 for lowering Lp(a) levels and for the treatment of a condition associated with elevated levels of Lp(a).

21. A composition according to claim 19 or 20, comprising N-(4-[3-(4-fluoro-benzenesulfonyl)-4-hydroxy-phenoxy]-3,5-dimethyl-phenyl)-oxamic acid or a pharmaceutically acceptable salt thereof and a statin selected from the group consisting of simvastatin, pitavastatin and fluvastatin or a pharmaceutically acceptable salt thereof.